

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS**

ABBOTT GMBH & CO., KG, )  
ABBOTT BIORESEARCH CENTER, INC., )  
AND ABBOTT BIOTECHNOLOGY LTD., )

Plaintiffs, )

v. )

C.A. No. 4:09-CV-11340 (FDS)

CENTOCOR ORTHO BIOTECH, INC. AND )  
CENTOCOR BIOLOGICS, LLC., )

Defendants. )

JURY TRIAL DEMANDED  
**PUBLIC REDACTED VERSION**

**DEFENDANTS' SUPPLEMENTAL CLAIM CONSTRUCTION BRIEF**

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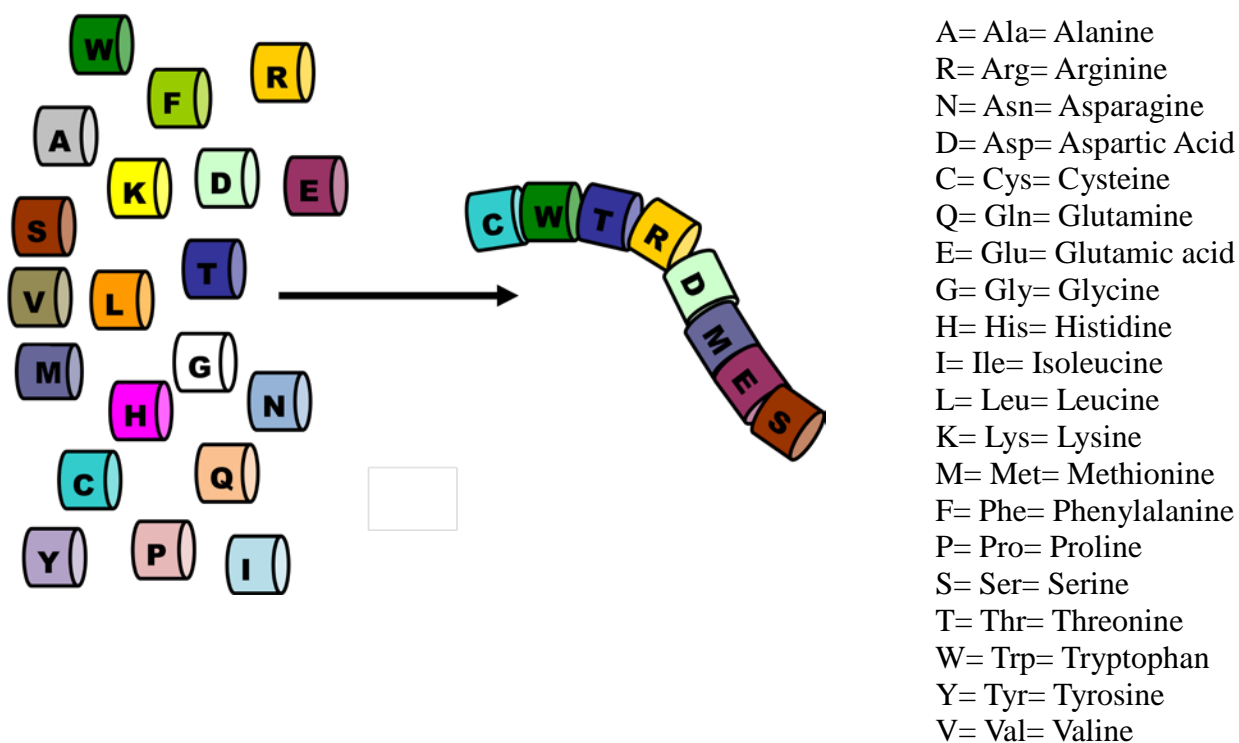
In the March 16 status conference in this case, the Court informed the parties that the construction of the claim term “human antibody” would be considered on the merits. The Court then invited additional briefing on the merits.

As set forth in more detail below, Centocor’s proposed construction of “human antibody” is taken from the express language of the asserted patents and provides a practical definition for the term. Abbott’s proposed construction, by contrast, has no foundation in the patent itself and provides no meaningful clarification on the construction of the term “human antibody.”

## I. TECHNICAL BACKGROUND

### A. Antibodies Are Proteins Made Of Amino Acid Building Blocks

Antibodies are proteins made by the immune systems of humans, mice, and other animals, that allow the animal to detect and neutralize foreign substances that enter the body; i.e., antigens. Like all proteins, antibodies are made of amino acid building blocks that are connected together by chemical bonds. The resulting string of amino acids is sometimes referred to as a protein chain. The following illustrates a chain of amino acids forming a protein:



There are only twenty different naturally-occurring amino acids (and each can be represented by either a single letter in the alphabet or a three letter code, as shown above). But many different protein chains can be built from these building blocks. Each different protein will have a different combination of amino acids. The order in which amino acids are strung together, called the amino acid sequence, distinguishes one protein from other proteins. As set forth in the patents-in-suit, the amino acid sequence is used to distinguish one antibody from another.

**B. DNA Provides The Instructions That Determine The Sequence Of Amino Acids In A Protein**

The amino acid sequence for a particular antibody generated by our natural immune system is based on instructions in our DNA. In a mammalian cell, a DNA sequence directs the cell to make a specific amino acid sequence through a process that is generally referred to as gene expression. That process of taking the DNA instructions and building a protein chain involves a series of chemical reactions, including the transcription of DNA into RNA and the translation of RNA into an amino acid sequence. The mammalian cell has the machinery to run the process, allowing it to accept DNA instructions and build an amino acid sequence.

**C. DNA Provides Instructions For Germline Amino Acid Sequences**

The pieces of DNA that carry instructions for building amino acid sequences are called genes. We inherit our genes from our parents. The genes that we inherit from each of our parents encode for human “germline” amino acid sequences. Similarly, the genes that a mouse inherits from its parents encode for mouse “germline” amino acid sequences.

Looking at a germline amino acid sequence in isolation does not tell you whether that sequence was produced by a human, a mouse, or some other mammal, because the same 20

amino acids are used to build all mammalian proteins. This is illustrated by comparing the following:

Example of a human germline antibody sequence (Pearson Decl. Ex. 1, Kabat *et al.* at 317)<sup>1</sup>:

**QVQLQESGPGLVKPSDTLSLTCAVSGYSISSSNWWGWIRQPPGKGLEWI  
GYIYYSGSTYYNPSLKSRVTMSVDTSKNQFSLKLSSVTAVDTAVYYC...**

Example of a mouse germline antibody sequence (*id.* at 433):

**EVKLVESGGGLVQPGGSLSLSCAASGFTFTDYYMSWVRQPPGKALEWL  
ALIRNKANGYTTEYSASVKGRFTISRDNQSILYLQMNALRAEDSATYY  
CA...**

Example of a rabbit germline antibody sequence (*id.* at 514):

**QSVEESRGGLIKPTDTLTCTVSGFSLSSYGVIWVRQAPGNLEYIGTI  
GSSGSAYYASWAKSRSTITRNTNLNTVTLKMTSLTAADTATYFCA...**

Since the same twenty amino acids are found in all of these proteins, more than just the sequence of amino acids is needed to be able to determine whether a particular antibody is a “human” or a “mouse” or a “rabbit” antibody, for example. One way to determine whether an antibody is “human” – the way Abbott describes in its patents – is to compare an antibody amino acid sequence with other *known* human antibody amino acid sequences.

#### **D. Abbott Used Genetic Engineering Techniques to Change The Amino Acids That Make Up An Antibody**

Through genetic engineering techniques, scientists can change the amino acids that make up an antibody. Scientists can do this, in the laboratory, by changing the DNA instructions that

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<sup>1</sup> As noted in Centocor’s Motion for Leave to Amend Its Claim Construction Proceedings, Kabat et al. published a book (four volumes) in 1991 that is referenced in the patents in suit and that listed known germline amino acid sequences of human antibodies as well as other species’ antibodies. Kabat lists known germline amino acid sequences by a three-letter amino acid code. For ease of reference, those three letter designations have been converted to single letter designations.

direct a cell to make an antibody. Abbott's work on J695 reflected in the asserted patents was the result of changing amino acids in an antibody called "Joe 9," as described below.

### **1. First, An Antibody Was Identified**

As one of the first steps in this process, scientists identify an antibody that seems to have potential for the intended purpose. Methods for doing this were known and published well before Abbott filed the applications that issued as the patents-in-suit. Scientists had created human phage display libraries that included pieces of DNA isolated from blood or other tissue samples (such as from tonsils) taken from human donors (see, Pearson Decl. Ex. 2, 128 patent at 103:28-31, citing Vaughan et al., (1996) *Nature Biotech.* 14:309-14), and had been screening those libraries to identify antibodies<sup>2</sup> that bind to a particular antigen (*id.* at 39:55-40:9, citing, for example, Clackson et al. (1991) *Nature* 352:624-628). This technique had, in fact, been used and published years before the filing date for the asserted patents to identify antibodies to human antigens (*id.* at 39:55-40:8, citing, for example, Griffiths et al. (1993) *EMBO J.* 12:725-34), as acknowledged in the patent specifications:

#### **II Selection of Recombinant Human Antibodies**

Recombinant human antibodies of the invention can be isolated by screening of a recombinant combinatorial antibody library . . . .  
Methodologies for preparing and screening such libraries are known in the art.

(*Id.* at 39:54-61).

The patents describe "Joe 9" as an antibody that was originally found by screening a phage display library for antibodies that bind to IL-12 (*id.* at 30:64 – 31:6). The methods for doing this were "known in the art" (*id.* at 39:55-61)

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<sup>2</sup> The term "antibodies" is used here as shorthand. These phage libraries really contain only the binding part of antibodies that, once selected, can be coupled to a known antibody framework (Pearson Decl. Ex. 2 at 103:23-28)

## **2. Then the Amino Acid Sequence Was Changed To Improve The Desired Properties**

Joe 9, the name given by the Abbott inventors to an antibody identified by screening an established phage display library, was a low affinity antibody (*id.* at 31:4-6). To develop antibodies with improved binding affinities, Abbott then generated a series of antibodies based on Joe 9 in which the amino acid sequence in the binding regions (CDR's) of Joe 9 were changed (*id.* at 31:6-13; *see also* 104:39-41 (“In order to increase the affinity of Joe 9, various mutations of the complementary determining region 3 (CDR3) of both the heavy and light chains were made.”). They did this through a known process called site-directed mutagenesis (*id.* at 29:18-19; 104:41-55).

Site-directed mutagenesis involves a standard set of procedures developed by scientists for changing the DNA instructions for protein sequences in the laboratory (*id.* at 68:9-15). The result is that one or more amino acids in the amino acid sequence of an antibody can be changed. (*id.* at 29:14-16). The patents define the phrase “selective mutagenesis approach” as including “a method of improving the activity of an antibody by selecting and individually mutating” amino acids in the binding regions (CDR's) of the antibody (*id.* at 29:56-60).

## **3. The Patents Specifically Describe One Lineage Of Antibodies Starting With “Joe 9” Where Amino Acids Were Modified To Improve Desired Properties**

As set forth above, the patents describe a lineage of antibodies that starts with Joe 9, where the Joe 9 amino acid sequence was modified and the properties of the resulting antibodies were tested (*id.* at 31:53-32:65). One of the antibodies generated through this laboratory manipulation of amino acid sequences – “Y61” – demonstrated a significant improvement in binding affinity (*id.* at 31:15-18).



But the inventors made more changes to individual amino acid residues in the binding regions (CDR's) of Y61. The final antibody in the lineage described in the patents – “J695” – differs from its predecessor, Y61, by only two amino acids that were specifically changed with the goal of improving affinity (*id.* at 31:26-31). J695 is described in the patents:

A particularly preferred recombinant, neutralizing antibody of the invention, J695, was produced by site-directed mutagenesis of contact and hypermutation amino acids residues of antibody Y61 (see Example 2 and section III below). J695 differs from Y61 by a Gly to Tyr substitution in Y61 at position 50 of the light chain CDR2 and by a Gly to Tyr substitution at position 94 of the light chain CDR3.

(*Id.* at 36:43-49).

## **II. “HUMAN ANTIBODY” SHOULD BE CONSTRUED CONSISTENTLY WITH THE EXPRESS DEFINITION IN THE PATENTS**

Once the amino acid sequence of an antibody has been manipulated in the laboratory, it is not so clear-cut to classify the new non-natural antibody as human, or mouse, or rabbit, or something else. An antibody that has the same amino acid sequence as a specified human germline antibody sequence can be characterized as human. But as scientists change amino acids one by one, when does the antibody change from being a “human” antibody to something non-human? This is a somewhat controversial matter, and scientists can disagree in the abstract about where to draw the line. But we need not reconcile the different theoretical approaches taken by scientists on this issue, because the asserted patents expressly define what it means to be a “human antibody” within the scope of the invention.

The way that the asserted patents do this is to define antibodies as human – or not human – by reference to specific human germline sequences for antibodies. According to the express definition, at least for purposes of these patents, an antibody is a “human antibody” as long as it corresponds to a human germline sequence identified in a specific reference book (Kabat 1991) or has no more than 20 amino acid differences as compared to those human germline sequences.

**A. The Asserted Patents Give An Express Definition Of “Human Antibody”**

The asserted patents have a section that begins: “In order that the present invention may be readily understood, certain terms are first defined” (Pearson Decl. Ex. 2, 128 patent at 24:29-30). As stated in that definitions section, the term “human antibody” includes antibodies that correspond to the human germline amino acid sequences listed in a specific reference book (Kabat 1991) as well as those antibodies that differ by up to 20 amino acids from the specified germline sequences (*id.* at 26:55-27:6). Thus, the definition includes antibodies that are the same as germline *and* those whose sequences have been modified from germline, but it places a limit on how many modifications can be made. This is stated in a paragraph spanning columns 26 and 27 of the 128 patent, as follows:

The term “*human antibody*” includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat *et al.* (See Kabat, *et al.* (1991) *Sequences of proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-directed mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. The mutations preferably are introduced using the “selective mutagenesis approach” described herein. The human antibody can have at least one position replaced with an amino acid residue, e.g., an activity enhancing amino acid residue which is not encoded by the human germline immunoglobulin sequence. ***The human antibody can have up to twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence.*** In other embodiments, up to ten, up to five, up to three or up to two positions are replaced. In a preferred embodiment, these replacements are within the CDR regions as described in detail below. However, the term “human antibody,” as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

(*Id.* at 26:55-27:13, emphasis added).

Notably, Abbott has never suggested that this definition does *not* describe a human antibody, as that term should be understood in the context of the asserted patents. And Abbott

does not dispute that its expert, Dr. Iverson, interpreted this same section as providing a definition of “human antibody” in the interference proceedings (Abbott Opp. Br. at 13).<sup>3</sup> But Abbott has pointed to the word “includes” in this paragraph as suggesting that the description is exemplary and not limiting.

Granted, the term “includes,” when considered in a vacuum, may not suggest any outer limits on what is encompassed within the definition. But it means something different in the context of the paragraph spanning columns 26 and 27 of the 128 patent. Here, it is coupled with a statement that limits “the human antibody” to one having no more than twenty positions replaced with amino acid residues that are not part of the human germline sequence.

As previously noted, saying that the Pittsburgh Steelers team *includes* Ben Roethlisberger and Troy Polamalu would not exclude any number of other players from being on the team. This is Abbott’s argument. But that ignores the rest of the paragraph that is part of the definition. Saying that the Pittsburgh Steelers team *includes* Ben Roethlisberger and Troy Polamalu, and also stating that the team *can have up to* 53 total players, provides a clear outer limit on the team size. The definition of “human antibody” provides the same kind of limit on the number of amino acid positions that can be different from human germline sequences, and still be considered a human antibody:

The term “human antibody” *includes* antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat, et al. (1991) . . . . The human antibody *can have up to* twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence. . . . .

(Pearson Decl. Ex. 2, 128 patent at 26:55-27:13, emphasis added).

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<sup>3</sup> Abbott agrees that its expert, Dr. Iverson, adopted parts of the language in columns 26 and 27 as a definition of “human antibody” in the interference proceedings, but argues that it only relied on the latter part of the definition for purposes of distinguishing over the prior art during prosecution (Abbott Opp. Br. at 13-14).

**B. Abbott's Proposed Definition Of Human Antibody Has No Intrinsic Support And Provides No Practical Definition For The Term**

Apparently recognizing that there needs to be some definition to this term that links the amino acid sequence to some human reference, Abbott has proposed that the term “human antibody” be defined, not by the antibody’s structure (*i.e.*, comparing its amino acid sequence to known human amino acid sequences), but by how it is made. Specifically, Abbott proposes that “human antibody” mean “an antibody that is derived from human DNA and not from the DNA of any non-human species.” But this has no support in the intrinsic evidence, and using the term “derived” does not provide meaningful clarity to the definition.<sup>4</sup>

Scientists could, for example, start with a human germline antibody sequence and, using site-directed mutagenesis, change the amino acids one-by-one to create a new sequence that is close to, or even exactly the same as, a natural mouse germline sequence. Should that antibody be classified as a human antibody or a mouse antibody? Using Abbott’s definition, this naturally occurring mouse antibody would be a human antibody. So it is not enough to say that it was “derived” from a human antibody without placing any limits on how much of the sequence can be changed in the laboratory. That is why the patents expressly define “human antibody” by comparing them to known antibody structures.

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<sup>4</sup> Also unsupported is Abbott’s argument that Centocor somehow agreed in the interference proceedings that the Stelara antibody met Abbott’s definition of a human antibody. Abbott is incorrect. The referenced exchange was directed to *Centocor’s claim 1*, and Centocor’s patent application provided an entirely different definition of “human antibody” as an antibody in which substantially every part of the protein is substantially non-immunogenic in humans (Pearson Decl. Ex. 3, Application 10/912,994 at COBI00626341, lines 29-31). That definition has no relevance to the interpretation of Abbott’s claims. Abbott’s claims must be interpreted in light of Abbott’s specification.

**C. Abbott's Criticism Of Centocor's Proposed Definition Is Unfounded**

Abbott suggested in its brief that applying the definition of "human antibody" that Centocor has proposed would exclude embodiments described in the patents. That is not supported by the patent or by the testimony in this case.

There is no intrinsic evidence (in the asserted patents or prosecution histories) about whether the Abbott embodiments (for example, the antibodies they identify as Joe 9 and J695 and describe in the specifications) are within twenty amino acids from Kabat human germline sequences published in 1991. The only comparison provided in the patent compares Joe 9, J695, and other related antibodies to a different compilation of sequences that are in the VBASE database. That comparison does not shed any light on whether the Joe 9 and/or J695 antibody embodiments fall within the definition of "human antibody."

**1. The 1991 Kabat Compilation Was Specifically Selected As The Reference For Comparison**

The fact that the patents, outside of the definitions section, refer to the VBASE database of sequences provides further evidence that the selection of the 1991 Kabat listing in the definitions section was intentional. The Abbott inventors clearly knew that other sequence compilations existed, but chose to use the 1991 Kabat compilation for purposes of their definition of human antibody and chose twenty as the limit on the number of amino acid changes. Kabat is not just an exemplary reference; it is the reference that the Abbott inventors chose for purposes of setting a benchmark.

It cannot be the case, as Abbott now suggests, that any database will do, including those that have been updated up through and past the date on which the patents were filed. The patents specifically point to the Kabat germline sequences published in 1991 as those that should be used for the comparison. Scientists in the field are entitled on to rely on the reference that the

inventors specifically identified. If Abbott's argument were to prevail, the scope of the patent claims could conceivably have expanded after the filing date because of additional known, human sequences being added to a database. That cannot be the case. The words in a claim are given the meaning they had at the time of the invention, and should not be broadened to cover new discoveries. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005); *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1353-54 (2000).

The selection of the Kabat germline sequences as the point of reference was not accidental. Michael White, one of the inventors of the 128 and 485 patents, [REDACTED]  
[REDACTED]  
[REDACTED] (Pearson Decl. Ex. 4, White Tr. at 63:12-16; Pearson Decl. Ex. 5 at ABT-IL12-03151780). [REDACTED]  
[REDACTED] (Pearson Decl. Ex. 4, White Tr. at 64:16-19, 68:14-19; Pearson Decl. Ex. 5 at ABT-IL12-03151780 [REDACTED]  
[REDACTED]  
[REDACTED] (Pearson Decl. Ex. 4, White Tr. at 69:22 – 70:15). Thus, according to inventor White, [REDACTED]  
[REDACTED] (*id.* at 71:3-8).

So the selection of the Kabat germline sequences as the point of reference was based on the work that the named inventors were doing at the time. [REDACTED]  
[REDACTED]  
[REDACTED] (*i.e.*, would reduce adverse reactions in patients given this

antibody as a therapeutic) (*id.* at 74:10-17). [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] (*id.* at 79:14-19, referring to Pearson Decl. Ex. 6 at ABT-IL12-00008496-97). Thus, the inventors made their other embodiments, including J695, even closer to germline. Like Joe 9, those embodiments are “human antibodies” according to the definition in the patents. Although this evidence of Mr. White’s and the other inventors’ work is not evidence intrinsic to the patent, it confirms that the inventors intentionally selected the Kabat sequences as the point of reference in their definition of “human antibody.”

## **2. Centocor’s Proposed Definition Does Not Exclude Described Embodiments**

Based on its prior brief, it appears that, notwithstanding the contrary testimony from one of its inventors, Abbott may attempt to argue that Joe 9 and/or J695 would not meet the express definition of “human antibody” that is included in the patents because their amino acid sequences differ from germline sequences in a different database, the VBASE database. But Abbott did not refer to the VBASE database when defining “human antibody;” it referred to the Kabat database. And, to the extent any extrinsic evidence is considered on this subject, the comparison by an inventor to the closest Kabat germline sequences, and his conclusion that the described embodiments fall within the scope of the express definition of “human antibody” that spans columns 26 and 27 of the 128 patent, as recorded contemporaneously in his laboratory notebook written years before this litigation, should be given more weight than any new, litigation-induced evidence.

**3. The Definition Of Human Antibody Refers To Differences In Amino Acids Of The Antibody, Not Just Portions Of The Antibody**

Also off the mark is Abbott's suggestion that a person of ordinary skill in the art would only count differences in the framework regions of an antibody, and not the complementarity determining regions (CDRs), in comparing a sequence to germline (Abbott Opp. Br. at 12 n.5). The express definition of human antibodies indicates that the differences in the CDRs count:

The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-directed mutagenesis in vitro or by somatic mutation in vivo), for example *in the CDRs and in particular CDR3*. The mutations preferably are introduced using the "selective mutagenesis approach" described herein.

(Pearson Decl. Ex. 2, 128 patent at 26:61-65, emphasis added).

Abbott is also incorrect in suggesting that only a fragment of an antibody should be compared to germline. In the patents, "antibody" is defined as having "four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds" (*id.* at 24:46-49). It is that "antibody" that "can have up to twenty positions replaced with amino acid residues which are not part of the human germline sequence" (*id.* at 27:4-6).

**III. CONCLUSION**

Centocor's proposed construction of "human antibody" is taken from the express language of the asserted patents and provides a practical definition for the term. This term should be construed as follows:

A human antibody includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat, et al. (1991) *Sequences of proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242), but the antibody can have up to twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence.



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**CERTIFICATE OF SERVICE**

The undersigned hereby certifies that a true and correct copy of the foregoing Defendants' Supplemental Claim Construction Brief was electronically mailed to the following counsel of record on March 28, 2011 through the Court's ECF notification system.

/s/Matthew Pearson